Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Monohydrous dihydrogen phosphate salts of norfloxacin and ciprofloxacin

Benyong Lou,[a] Dan Boström[b] and Sitaram P. Velaga[a]*

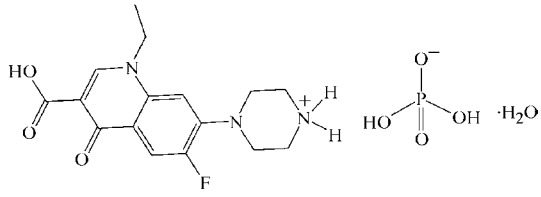
[a]Department of Health Science, Luleå University of Technology, Luleå S-971 87, Sweden, and [b]Energy Technology and Thermal Process Chemistry, Umeå University, Umeå S-901 87, Sweden
Correspondence e-mail: sitaram.velaga@ltu.se

Received 18 September 2007
Accepted 25 October 2007
Online 24 November 2007

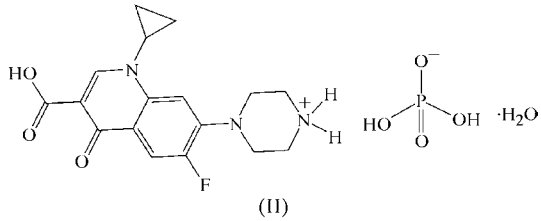
Norfloxacin and ciprofloxacin crystallize with phosphoric acid in aqueous solution to give the salts 4-(3-carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-7-quinolyl)piperazinium dihydrogenphosphate monohydrate, $C_{16}H_{19}FN_3O_3^+\cdot H_2PO_4^-\cdot H_2O$, and 4-(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-7-quinolyl)piperazinium dihydrogenphosphate monohydrate, $C_{17}H_{19}FN_3O_3^+\cdot H_2PO_4^-\cdot H_2O$, respectively. In the crystal structures, the phosphate anions and the piperazine rings of norfloxacin or ciprofloxacin form a 12-membered supramolecular synthon, *viz*. $R_4^4(12)$. The synthons $R_4^4(12)$ and $R_2^2(8)$ formed between adjacent phosphate anions result in the three-dimensional structures.

Comment

The design and synthesis of multicomponent crystals of active pharmaceutical ingredients (APIs) has attracted considerable attention in recent years (Almarsson & Zaworotko, 2004; Childs *et al.*, 2007). Many types of supramolecular synthons have been exploited for generating multicomponent crystals by the use of suitable guest molecules with complementary functional groups to APIs (Trask *et al.*, 2005; Wenger & Bernstein, 2006). Although an organic acid is preferable to a basic drug molecule, an inorganic acid, such as phosphoric acid, displays its unique hydrogen-bonding pattern in the formation of multicomponent crystals (Chen *et al.*, 2007). We treated norfloxacin and ciprofloxacin with phosphoric acid in aqueous solution and prepared the title compounds, (I) and (II), respectively, in which phosphoric acid participates in different supramolecular synthons.



(I)



(II)

The crystal structure of (I) contains one norfloxacin cation, one dihydrogenphosphate anion and one water molecule in the asymmetric unit. Difference Fourier maps show that phosphoric acid transfers one H atom to the piperazine ring N atom of norfloxacin, thus forming the dihydrogenphosphate salt of norfloxacin. The carboxylic acid group of norfloxacin is involved in intramolecular hydrogen bonding with the quinolone O atom (O2—H2···O3; Table 1). The piperazine ring N atom of norfloxacin is hydrogen bonded to two symmetry-dependent phosphate anions ($N1^+$—H1*A*···O4^{iv} and $N1^+$—H1*B*··· O5; symmetry codes as in Table 1), and this results in a neutral tetramer based on a 12-membered supramolecular synthon, *viz*. $R_4^4(12)$ (Fig. 1). The solvent water molecule interacts with the phosphate anion through two types of hydrogen bonds (O8—H8*A* ···O5 and O7—

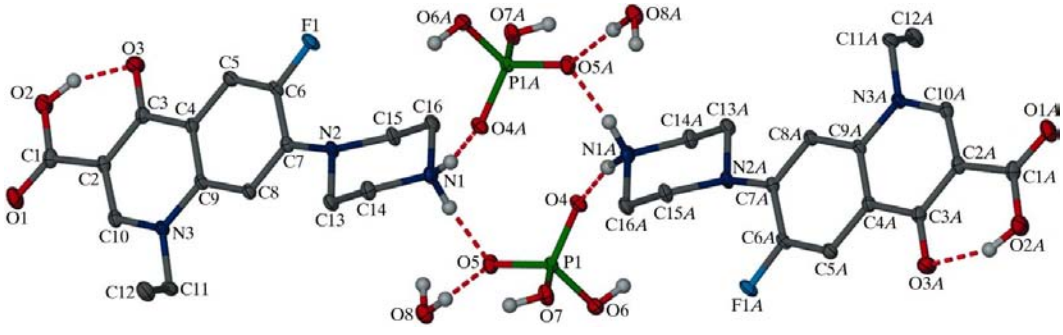


Figure 1
The structure of (I), shown with 30% probability displacement ellipsoids. Dashed lines indicate hydrogen bonds. H atoms on C atoms have been omitted for clarity. Atoms labeled with the suffix '*A*' are at the symmetry position $(1 - x, -y, 2 - z)$.

 DOI: 10.1107/S0108270107053218 © 2007 International Union of Crystallography

H7···O8^{iii}; Table 1) to give another 12-membered supramolecular synthon, *viz*. $R_4^4(12)$. Two adjacent phosphate anions also form a homosynthon, *viz*. $R_2^2(8)$, through hydrogen bonding (O6—H6···O4^{ii}; Table 1). Along the [110] direction, the two synthons result in a one-dimensional hydrogen-bonded chain containing phosphate anions and solvent water molecules (Fig. 2). The water molecule is also hydrogen bonded to the carboxylic acid group of norfloxacin (O8—H8*B*···O2^{i}; Table 1). As a result, phosphoric acid and water molecules link norfloxacin into a three-dimensional structure through three types of supramolecular synthon (Fig. 3).

The structure of (II) is very similar to that of (I). It contains one ciprofloxacin cation, one dihydrogenphosphate anion and one water molecule in the asymmetric unit (Fig. 4). In the crystal structure, phosphoric acid again transfers one H atom to the piperazine ring N atom of ciprofloxacin, forming a similar 12-membered supramolecular synthon, $R_4^4(12)$. A similar one-dimensional chain along the [110] direction, including phosphate anions and water molecules, is formed. Three similar supramolecular synthons result in the three-dimensional structure (Fig. 5). The hydrogen-bond geometry in (II) is given in Table 2.

Several dicarboxylate salts of norfloxacin have been reported recently (Basavoju *et al.*, 2006). For example, in the structure of the succinate salt of norfloxacin, the carboxylate group of succinic acid and the piperazine rings of norfloxacin form a supramolecular $R_4^4(12)$ synthon. In the structure of the hydrated lactate salt of ciprofloxacin (Prasanna & Guru Row, 2001), centrosymmetrically related lactate anions and water molecules form a two-dimensional hydrogen-bonded sheet which links ciprofloxacin into a three-dimensional network. Compared with these organic salt formers, phosphoric acid displays more flexible hydrogen-bonding patterns through participating in three kinds of supramolecular synthons in (I) and (II).

In conclusion, norfloxacin and ciprofloxacin crystallize with phosphoric acid in aqueous solution to give their dihydrogenphosphate monohydrate salts. In the crystal structures, the phosphate anions and water molecules link norfloxacin or ciprofloxacin into three-dimensional structures through three types of supramolecular synthons. The structures show that phosphoric acid could be a good candidate for forming multicomponent crystals of APIs, as it can provide various hydrogen-bonding interactions.

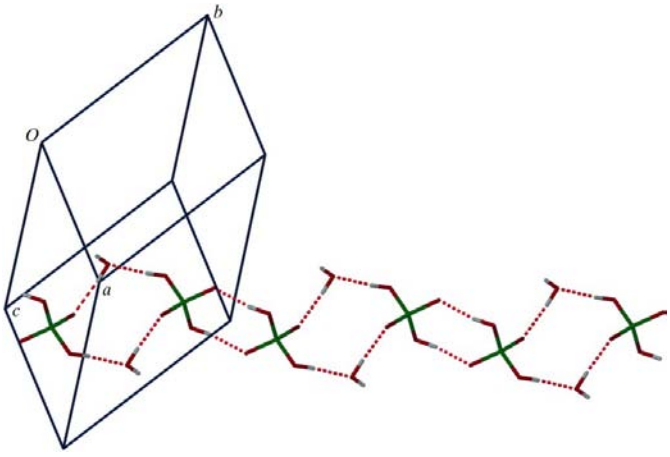


Figure 2
The one-dimensional chain of phosphate anions and water molecules along the [110] direction. Dashed lines indicate hydrogen bonds.

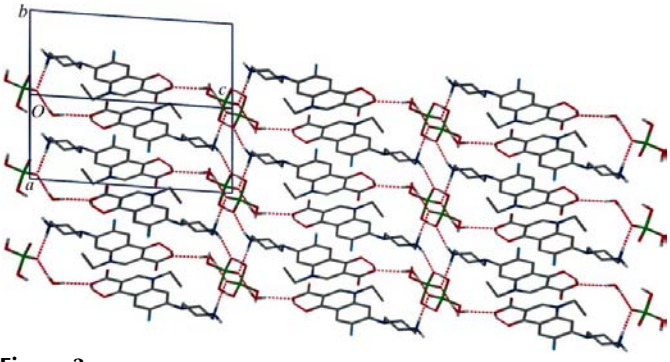


Figure 3
The three-dimensional structure of (I), viewed along the [110] direction. Dashed lines indicate hydrogen bonds.

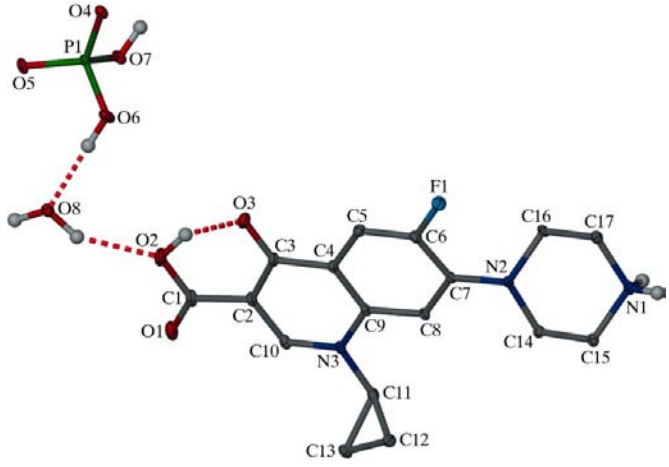


Figure 4
The structure of (II), shown with 30% probability displacement ellipsoids. Dashed lines indicate hydrogen bonds. H atoms on C atoms have been omitted for clarity.

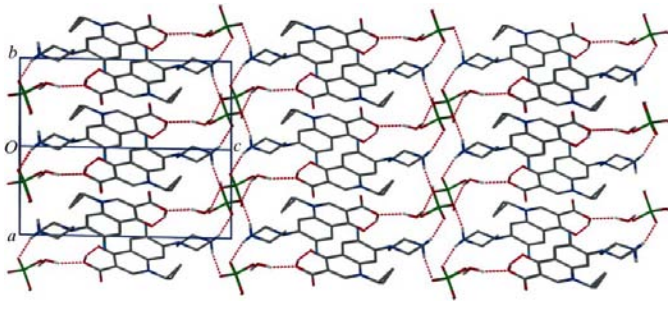


Figure 5
The three-dimensional structure of (II), viewed along the [110] direction. Dashed lines indicate hydrogen bonds.

Experimental

For the preparation of (I), a mixture of norfloxacin (0.032 g, 0.1 mmol) and phosphoric acid (0.020 g, 0.2 mmol) in water (10 ml) was heated until dissolved. The solution was kept in a fume hood and colorless crystals were obtained after several days. Differential scanning calorimetry showed two endothermic peaks at 405 and 543 K, respectively. Compound (II) was prepared as (I) except that ciprofloxacin was used instead of norfloxacin. Differential scanning calorimetry showed two endothermic peaks at 406 and 529 K, respectively.

Compound (I)

Crystal data

$C_{16}H_{19}FN_3O_3^+\cdot H_2PO_4^-\cdot H_2O$
M_r = 435.34
Triclinic, $P\overline{1}$
a = 7.1918 (14) Å
b = 8.9400 (18) Å
c = 15.792 (3) Å
α = 103.81 (3)°
β = 94.01 (3)°
γ = 106.51 (3)°
V = 934.9 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.21 mm^{-1}
T = 100 (2) K
0.25 × 0.20 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer
10002 measured reflections
5425 independent reflections
4398 reflections with $I > 2\sigma(I)$
R_{int} = 0.030

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.146
S = 1.10
5425 reflections
263 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.65 e Å^{-3}
$\Delta\rho_{min}$ = −0.94 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O3	0.84	1.69	2.482 (2)	156
O8—H8A···O5	0.84	1.85	2.6783 (19)	172
O8—H8B···O2^{i}	0.84	2.04	2.807 (2)	151
O6—H6···O4^{ii}	0.84	1.99	2.566 (2)	125
O7—H7···O8^{iii}	0.84	2.21	2.623 (2)	110
N1—H1B···O5	0.88	1.83	2.706 (2)	172
N1—H1A···O4^{iv}	0.87	1.86	2.714 (2)	167

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x, -y, -z+2$; (iii) $-x+1, -y+1, -z+2$; (iv) $-x+1, -y, -z+2$.

Compound (II)

Crystal data

$C_{17}H_{19}FN_3O_3^+\cdot H_2PO_4^-\cdot H_2O$
M_r = 447.35
Triclinic, $P\overline{1}$
a = 7.2582 (15) Å
b = 8.9979 (18) Å
c = 15.712 (3) Å
α = 100.93 (3)°
β = 96.00 (3)°
γ = 105.74 (3)°
V = 956.4 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.21 mm^{-1}
T = 100 (2) K
0.26 × 0.22 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer
9764 measured reflections
5568 independent reflections
4311 reflections with $I > 2\sigma(I)$
R_{int} = 0.041

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.075
$wR(F^2)$ = 0.242
S = 1.12
5568 reflections
271 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 1.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.84 e Å^{-3}

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O3	0.84	1.74	2.529 (4)	155
O6—H6···O8	0.84	1.99	2.625 (3)	131
O7—H7···O4^{i}	0.84	1.96	2.556 (3)	128
O8—H8A···O2	0.86	2.08	2.881 (3)	154
O8—H8B···O5^{ii}	0.86	1.83	2.681 (3)	171
N1—H1A···O5^{iii}	0.86	1.84	2.695 (3)	169
N1—H1B···O4^{iv}	0.87	1.89	2.726 (3)	163

Symmetry codes: (i) $-x+2, -y+1, -z$; (ii) $-x+1, -y, -z$; (iii) $x+1, y+1, z+1$; (iv) $-x+2, -y+2, -z+1$.

For both structures, H atoms bonded to N and water O atoms were located in difference maps and were refined as riding with N/O—H distances of 0.84–0.88 Å [U_{iso}(H) = 1.1–1.3U_{eq}(N,O)]. All other H atoms were positioned geometrically (C—H = 0.95–1.00 Å and O—H = 0.84 Å) and refined as riding, with U_{iso}(H) = 1.2U_{eq}(C,O) or 1.5U_{eq}(methyl C). The maximum residual electron density in (II) is larger than normally expected. The nearest atom to this maximum is atom P1 at a distance of 0.951 Å.

For both compounds, data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *X-SEED* (Barbour, 2001); software used to prepare material for publication: *SHELXL97*.

We are grateful for financial support from Norbottensforskningsråd (grant No. NoFo 05-011).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV3114). Services for accessing these data are described at the back of the journal.

References

Almarsson, Ö. & Zaworotko, M. J. (2004). *Chem. Commun.* pp. 1889–1896.
Barbour, L. J. (2001). *J. Supramol. Chem.* **1**, 189–191.
Basavoju, S., Boström, D. & Velaga, S. P. (2006). *Cryst. Growth Des.* **6**, 2699–2708.
Chen, A. M., Ellison, M. E., Peresypkin, A., Wenslow, R. M., Variankava, I. N., Savarin, C. G., Natishan, T. K., Mathre, D. J., Dormer, P. G., Euler, D. H., Ball, R. G., Ye, Z., Wang, Y. & Santos, I. (2007). *Chem. Commun.* pp. 419–421.
Childs, S. L., Stahly, G. P. & Park, A. (2007). *Mol. Pharm.* **4**, 323–328.
Nonius (1999). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Prasanna, M. D. & Guru Row, T. N. (2001). *J. Mol. Struct.* **559**, 255–261.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Trask, A. V., Motherwell, W. D. S. & Jones, W. (2005). *Cryst. Growth Des.* **5**, 1013–1021.
Wenger, M. & Bernstein, J. (2006). *Angew. Chem. Int. Ed.* **45**, 7966–7969.